REMARKS

Applicants respectfully request reconsideration of this application, and reconsideration of the Office Action dated February 21, 2003 (Paper No. 14). Upon entry of this Amendment, claims 1-9, 11-22 and 24-39 will remain pending in this application. Claims 10 and 23 has been cancelled. The amendments to the claims are supported by the specification and original claims. Particularly, the amendment to claim 1 is supported by the specification at page 15, line 24 through page 16, line 10 and original claim 10. No new matter is incorporated by this Amendment.

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Claims 1-39 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse.

The Office Action asserts that the phrase "which is stabilized towards ... to release biotin" in claim 1 is vague and indefinite. In response, Applicants have amended claim 1 to recite "said affinity ligand being connected to said linker 1 via an amide bond which is stabilized towards enzymatic cleavage." Applicants submit that claim 1, as amended, would be clear to those of ordinary skill in art.

The Office Action also asserts that the phrases "derivatives, mutants, and fragments" and "having essentially the same binding function to the affinity ligand." The Office Action asserts that the terms "derivatives, mutants, and fragments" encompass an innumerable amount of chemical possibilities and that the specification does not define these terms.

With respect to claims 4 and 30, Applicants have amended these two claims to remove the terms "mutants" and "derivatives." However, Applicants have not deleted the term "derivative" as Applicants again submit that those of ordinary skill would readily understand what is intended by the phrase. Claims 4 and 30 have been amended to recite "a derivative of avidin or streptavidin having essentially the same binding function to the

affinity ligand." Hence, the term "derivative" does not encompass an innumerable number of chemicals, but encompasses derivatives of avidin or streptavidin (which derivatives are known to those of ordinary skill) that have essentially the same binding function to the affinity ligand (e.g. biotin) as do avidin or streptavidin.

With respect to claim 5, Applicants submit that the specification provides numerous examples of biotin (see e.g., page 11 and claim 6). Thus, those of ordinary skill in the art would readily comprehend what is intended by the terminology "biotin derivative."

Now turning to claim 32, the Office Action asserts that claim 32 encompasses an innumerable number of chemicals. Applicants respectfully disagree, claim 32 encompasses derivates of EDTA or DTPA. Moreover, the specification includes examples of such derivatives on page 12. Thus, the term "EDTA derivatives" would be clear to those of ordinary skill.

The amendments to the claims and above remarks overcome this rejection. Hence, reconsideration and withdrawal of the rejection are respectfully requested.

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Claims 1-25 and 31-39 are rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Wilbur et al. (WO 97/29114). The Office Action asserts that Wilbur discloses every element of the claimed invention. Applicants respectfully traverse.

As stated in the previous Response, Wilbur fails to teach each and every element of the claimed invention and thus can not anticipate the claimed invention. Wilbur neither teaches nor fairly suggests a reagent which includes the three essential moieties recited in Applicants' invention, namely, an affinity label, an effector, and a biomolecule reactive moiety, and that is also designed to be protected against biotinidase wherein the biotinamide bond has been stabilized by introducing an alpha carboxylate or an N-methyl group into the linker.

Applicants' invention provides a reagent having three different moieties (an affinity label, an effector, and a biomolecule reactive moiety) each serving a specific need of simultaneously labeling of targeting molecules for in vivo diagnostic and therapeutic applications in conjunctions with extracoporeal removal of non-targeted molecules from blood circulation. Thus, since the reagent is to be used in vivo, the bonds provided by the linkers must be capable of resisting enzyme degradation. As detailed above, Wilbur neither teaches nor describes such a reagent.

Applicants also submit that this rejection is improper since Wilbur does not qualify as prior art under 35 U.S.C. 102(b). To qualify as prior art under 35 U.S.C. 102(b) a document must show, "(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States." *35 U.S.C. 102(b)*. Wilbur was published August 14, 1997. The present application is a continuation of PCT/SE98/01345 which was filed on July 7, 1998. Hence, the Wilbur document was neither patented nor described in a printed publication in this or a foreign country more than one year prior to the earliest date to which the present application is entitled. Hence, the rejection is improper and should be withdrawn.

The above remarks overcome this rejection. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

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Claims 26-30 are rejected under 35 U.S.C. § 103(a) as being obvious based on Wilbur et al. in view of Yau et al. (U.S. Pat. No. 5,541,287) or Theodore et al. (U.S. Pat. No. 5,578,287) and Maddock (U.S. Pat. No. 5,474,772). Applicants again respectfully traverse.

The deficiencies of Wilbur are discussed above. The secondary references cited in this rejection fail to remedy these deficiencies. None of the prior art of record teaches or

fairly suggests a method or kit that employs a reagent which includes an affinity label, an effector, and a biomolecule reactive moiety, and that is protected against biotinidase wherein the biotinamide bond has been stabilized by introducing an alpha carboxylate or an N-methyl group into the linker. Moreover, there is nothing in the prior art of record which would motivate those of ordinary skill in the art to design a reagent having each of the above noted characteristics. Hence, the prior art of record fails to render the claimed invention obvious.

The reagent of the present invention has been developed to solve the following problems, which occur when the targeting molecule (biomolecule) is equipped with both an effector and elements to facilitate the removal from the blood circulation by extracorporeal means. This novel reagent is intended to achieve certain objectives and improvements when used in conjunction with extracorporeal blood clearance which are discussed below.

1. Separate labeling of an effector moiety and affinity ligands is more prone to induce structural and conformational changes of the biomolecule and thereby changes the pharmacological properties including biodistribution as well as the solubility of the biomolecule. This is particularly true, when the affinity and effector moiety are linked through the same type of functional groups on the biomolecule. Today, the epsilon-amino groups are most commonly used. Applicants' reagent solves this problem by simultaneously conjugating an affinity ligand and an effector to the same functional group on the biomolecule.

2. Modification of biomolecules (e.g. proteins) in two separate steps results in a heterogeneous population of modified biomolecule in which the ratio of affinity ligand/effector units could differ from molecule to molecule. This results in a subgroup which will be readily removed from the blood circulation but will lack effect, as well as biomolecules that are highly efficacious but can not be removed from the blood circulation

due to the lack of affinity ligands. Applicants' reagent solves this problem by ensuring that each labeled molecule will carry a defined ratio of affinity ligand/effector agent, normally 1:1.

3. Biomolecules (e.g. proteins) are exposed to enzymatic cleavage. Separately labeled affinity and effector moieties are linked together through the back-bone structure of the biomolecule (e.g. proteins), which is readily exposed to enzymatic degradation. Hence, enzymatic cleavage could separate the two functions producing effector agents which are lacking the targeting properties as well as being detached from the affinity group, and are thereby unable to be removed from the blood circulation through the use of any affinity ligand. Applicants' reagent prevents such an undesirable side-effect from occurring by retaining the linkage of the affinity group and the effector regardless of the fate of the biomolecule *in vivo*.

4. Available reagents for biotinylation of proteins have a low solubility in aqueous buffers and normally increase the hydrophobicity of the biomolecule, making highly substituted biomolecules less water soluble. Furthermore, due to the hydrophobic nature of the spacer through which the biotin group is linked to a biomolecule, not all biotin groups are well exposed to the avidin interaction. Applicants' reagent circumvents these undesirable properties by carrying structural elements which improve the solubility and, at the same time, render a long spacer arm. This maximizes sufficient interaction with the immobilized receptor molecule.

5. In cases where the affinity ligand is linked to a trifunctional cross-linking moiety through an amide bond, such a bond can be susceptible to cleavage by enzymes others than non-proteolytic enzymes. The reagent of the present invention is furnished with an affinity ligand where the amide bond linking the affinity ligand to the linker is stabilized toward enzymatic cleavage. The reagent of the present invention exhibits structural

elements such as N-methyl or α-carboxyl groups to protect the amide bond from such enzymes.

The Office Action asserts that Wilbur teaches every element of the claimed invention except a method of diagnosing or treatment and kits. The Office Action also asserts that Yau, Theodore, and Maddock teach diagnosing and treatment methods and kits, and that by combining the teaching of these documents, it would be obvious to combine the teaching of the prior art thereby rendering the present invention obvious. Applicants respectfully disagree.

Theodore et al. and Yau et al. teach improved biotin-active agents intended to be used mainly in three-step pretargeting methods. Their focus is on synthesis of novel small organic molecules carrying a biotin group and radioactive isotopes bound to the organic molecule through a chelating group. Both documents recognize the disadvantage associated with *in vivo* administration of "targeting moiety-radioisotopic conjugates" for imaging and therapy is the localization of the attached radioactive agents to both non-target and target sites. However, there is no reference to any means of removing the "targeting moiety-radioisotope conjugate" from the blood circulation. Consequently, there is no reference to any such method and the documents are not helpful in addressing the above listed objectives of the present invention, nor do they give any guidance how to achieve the above objectives. The documents of Theodore and Yau do not address any of the above five objectives of the present invention, because these issues are not relevant in these particular treatment modalities.

Maddock teaches a method of blood clearance by extracorporeal means. The use of an avidin/biotin system for such purposes is described briefly in the text, but contrary to other extracorporeal systems, is not further discussed or exemplified. Maddock does not give any guidance as to how the biotinylation should be manufactured, nor does the document address any of the above listed objectives of this invention. Hence, any

combination of Wilbur, Theodore, Yau and Maddock will fail to arrive at the present invention, because none of the references includes the combination expressed in the claims, and there are no suggestions in any of the references that either address the above listed objectives or present solutions similar to those of the present invention or give any guidance how to arrive at the present invention.

The above remarks overcome this rejection. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

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Applicants respectfully submit that this Amendment and the above remarks obviate the outstanding objection and rejections in this case, thereby placing the application in condition for immediate allowance. Allowance of this application is earnestly solicited.

Furthermore, if the Examiner deems that this Amendment does not place the application in condition for allowance, the Examiner is respectfully requested to contact Applicants' undersigned representative to discuss any remaining issues.

If any fees are due in connection with the filing of this Amendment, such as fees under 37 C.F.R. §§1.16 or 1.17, please charge the fees to Deposit Account 02-4300; Order No. 033700.003.

Respectfully submitted,

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